

**Figure 1: Human IRS-1 protein sequence (SEQ ID NO: 1)**

1 masppesdgf sdvrkvgylr kpksmhkrff vltraaseagg parleyyene kkwrhkssap  
61 krsiplescf ninkradskn khlvalytrd ehfaiaadse aeqdswyqal lqlhnrakgh  
5 121 hdgaaalgag ggggscsgss glgeagedls ygdvppgpaf kevwqvilkp kglgqtknli  
181 giyrlcltsk tisfvklmse aaavvlqlmn irrcghsenf ffievgrsav tgpgefwmqv  
241 ddsvvaqnmh etileamram sdefrprskv qsssnscnpi svplrhhln nppsqsqvglt  
301 rrsrtesita tpsasmvggk pgsfrvrass dgegtmsrpa svdgspsvps tnrtahhrh  
361 gsarlhpln hrsipmpas rcspstspv slssstsg hgstsdclfr rssasvsgsp  
10 421 sdggfissde ygsspcdfsr sfrsvtpdsl ghtppargee elsnyicm gg kgpstltapn  
481 ghyilsrggn ghrctpgtgi gtspalagde aasaadldnr frkrthsagt sptithqktp  
541 sqssvasiee ytemmpaypp gggsggrlp ghrhsafvptr sypeeeglemh plerrgghr  
601 pdsstlhtdd gympmspgva pvpsgrkgs dympmspksv sapqqiinpi rrpqrvdpn  
661 gymmmspsgg cspdigggps ssssssnv sgtsyglwt ngvgghshv lphpkppves  
15 721 sggklpctg dymnm spvgd sntsspsdcy ygpedpqhkp vlsyyslpr fkhtrpgep  
781 eegarhqhlr lssgrlly aataddssss tssdsggy cgarleplp hphqvlqph  
841 lprkvdtaaq tnsrlarptr lsgdpkast lprareqqq qpllhppp kspgeyvnie  
901 fgdsqsgyls gpvafhssps vrcpsqlpa preeetgee ymkmdlgpgr raawqestgv  
961 emgrlgpapp gaasicrptr avpssrgdym tmqmscprqs yvdtspaapv syadmrtgia  
20 1021 aeevslprat maaassssaa sasptgpqga aelaahssll ggpqgggms aftrvnlspn  
1081 nqsakvira dpqgcrrrhs **setfsst**psa trvgntvpfg agaavggggg ssssedvkr  
1141 hssasfenvw lrp gelggap kepaklcgaa gglenglnyi dldlvkdfk cpqectpep  
1201 ppppppphqp lgsgessstr rssedlsaya sisfqkped rq

**Figure 2: Human IRS-2 protein sequence (SEQ ID NO: 2)**

1 maspprhgpp gpasgdgpnI nnnnnnnnhs vrkcgylrkq khghkrffvl rgpgaggdka  
61 tagggsapqp prleyyesek nwrskagapk rviaIdccIn Inkradpkhk yIalytkde  
121 yfavaaeneq eqegwyralt dlvsegraaa gdappaaapa ascsasIpga vgsagaaga  
5 181 edsyglvapa taayrevwqv nlkpkgIqqs knltgvyrIc IsartIgvk InceqpsvtI  
241 qImnIrIrcgh sdsffIevg rsavtgpgeI wmqaddsvva qnIhetIlea mkalkelfef  
301 rprsksqssg ssathpIsvp garrhhhlvn lppsqtglvr rsrtdsIaat ppaakcsscr  
361 vrtasegdgg aaagaaaaga rpvsvagspl spgpvrapIs rshtIlggr aagtkwhcfp  
421 agggIqhsrs msmpvehlpp aatspgslss ssdhgwgsyp pppgphlIp hplhhgpgqr  
10 481 pssgsasasg spsdpgfmsI deygsspgdI rafcsIrsnt pesiaetppa rdgggggefy  
541 gymtmdrpls hcgrsyrrvs gdaaqIdrg lkrtysltI parqrpvpqp ssasIdeytI  
601 mratfsgsag rIcpscpass pkvayhpye dygdieIgh rsssnlgad dgymptmpga  
661 alagsgsgsc rsddympmsp asvsapkqI qpraaaaaaa avpfagpagp aptfaagrtf  
721 pasgggykas spaesspedS gymrmwcgsk IsmehadgkI lpngdyInvs psdavttgtp  
15 781 pdffsaalhp ggeplrgvpg ccysslrsy kapytcggs dqvylmsspv grileeerle  
841 pqaIpgptqa asafgagptq pphpvvpspv rpsggrpegf Igqrgravrp trIslegIps  
901 lpsmheyplp pepkspgeyi nIdfgepgar Isppappla saassslls asspalsIgs  
961 gtpgtssdsr qrsplsdymn ldfsspkspk pgapsghpvg sIdgIIspea ssypplppr  
1021 psaspssslq ppppppapge lyrlppasav ataqqpgaas slsdtgdng dytemafgva  
20 1081 atppqpIaap pkpeaarvas ptsgvkrIsI meqvsgveaf lqasqppdph rgakviradp  
1141 **qggrrrhss**e **tfsttt**vtp vspsfahnpk rhnsasvenv slrksseggv gvgpgggdep  
1201 ptsprqlqa pplapqgrpw tpgqpgglvg cpgsggspmr retsagfqng lkyiaIdvre  
1261 epglppqpqp pppplpqpgd ksswgrtrsl ggIIsavgvg strggcggpg pgapapcptt  
1321 yaqh

25

30

Figure 3: Serine phosphorylation of IRS-1 in CHO/IR/IRS-1 cells

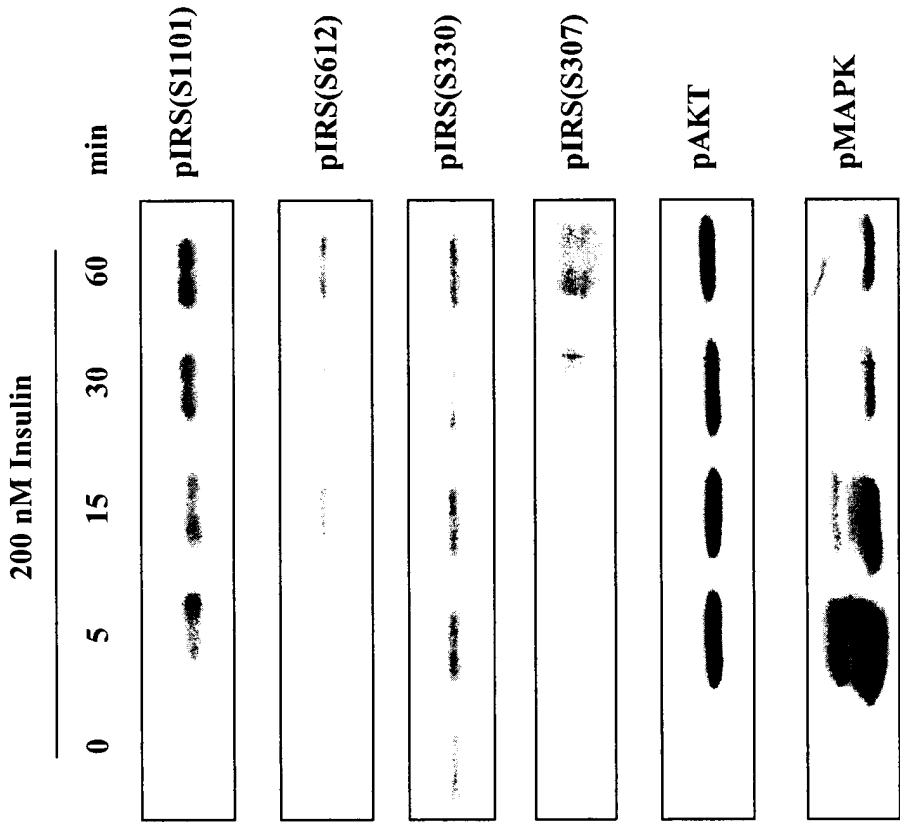
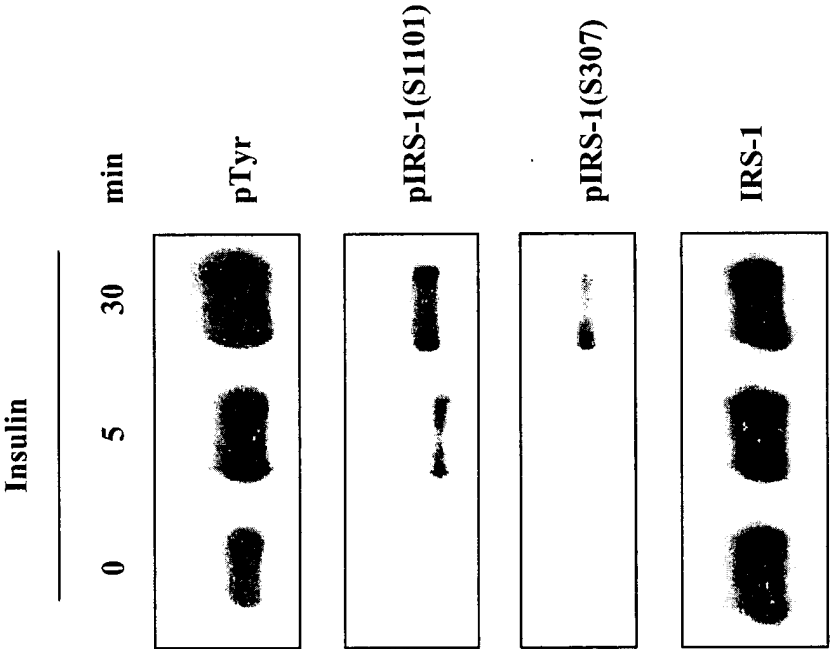


Figure 4: Phosphorylation of IRS-1 in 3T3L1 fat cells



**Figure 5: Phosphorylation of IRS-1 in L6 myocytes**

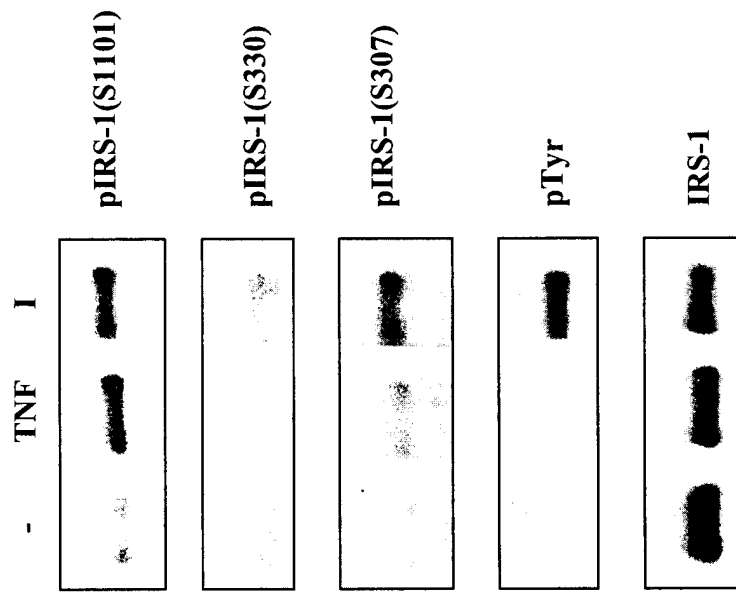


Figure 6: Specificity of pIRS-1(Ser1101) antibody

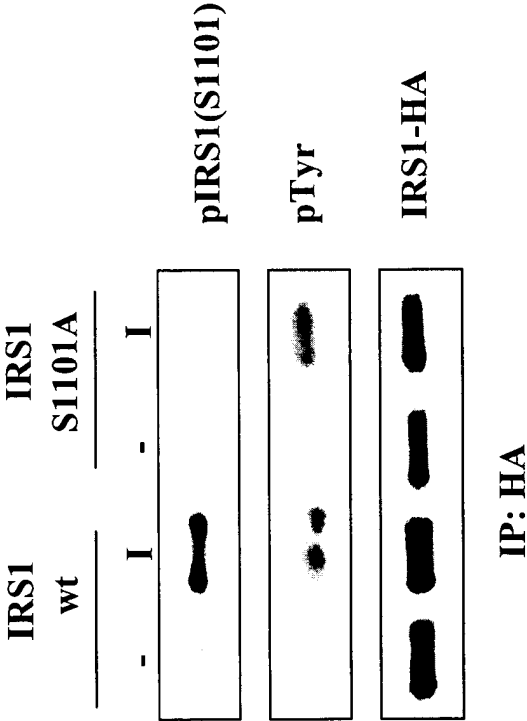
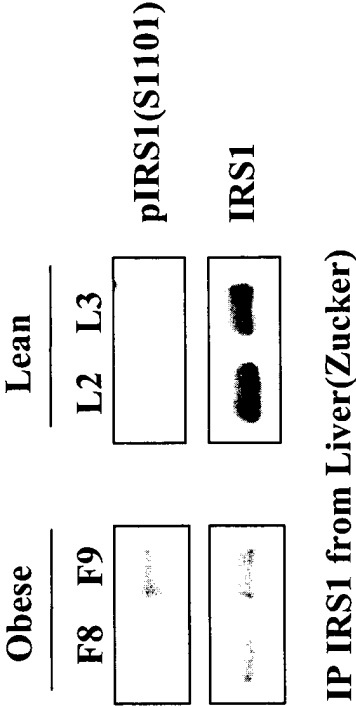


Figure 7: Phosphorylation of IRS-1 at Ser1101 in liver of Zucker rats



**Figure 8: Phosphorylation of IRS-2 at Ser1149 in CHO cells**

**IRS-1 S1101: GCRRRHS\*SETFSSTP**

**IRS-2 S1149: GRRRRHS\*SETFSSTT**

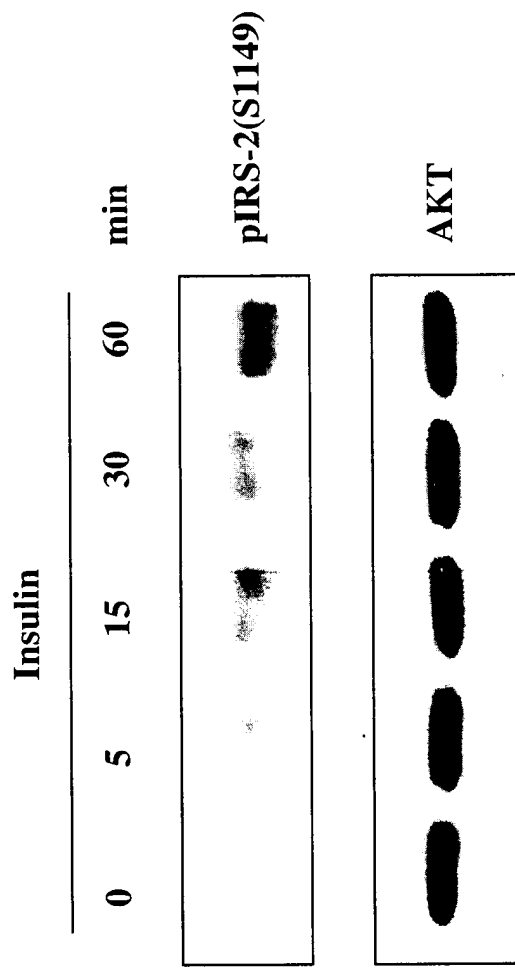




Figure 9: Phosphorylation of IRS1 at Ser1101 correlates with PKC activation

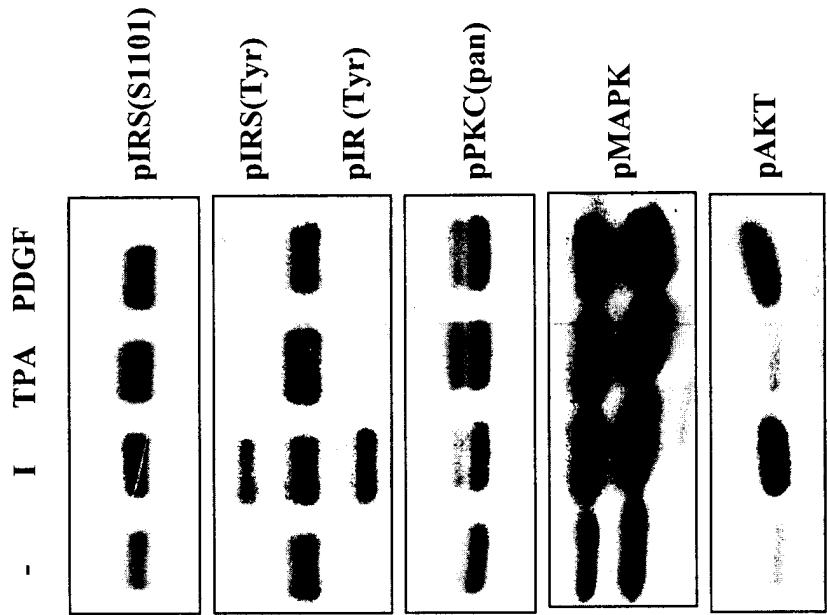


Figure 10: Phosphorylation of IRS1 at Ser1101 is blocked by PKC inhibition

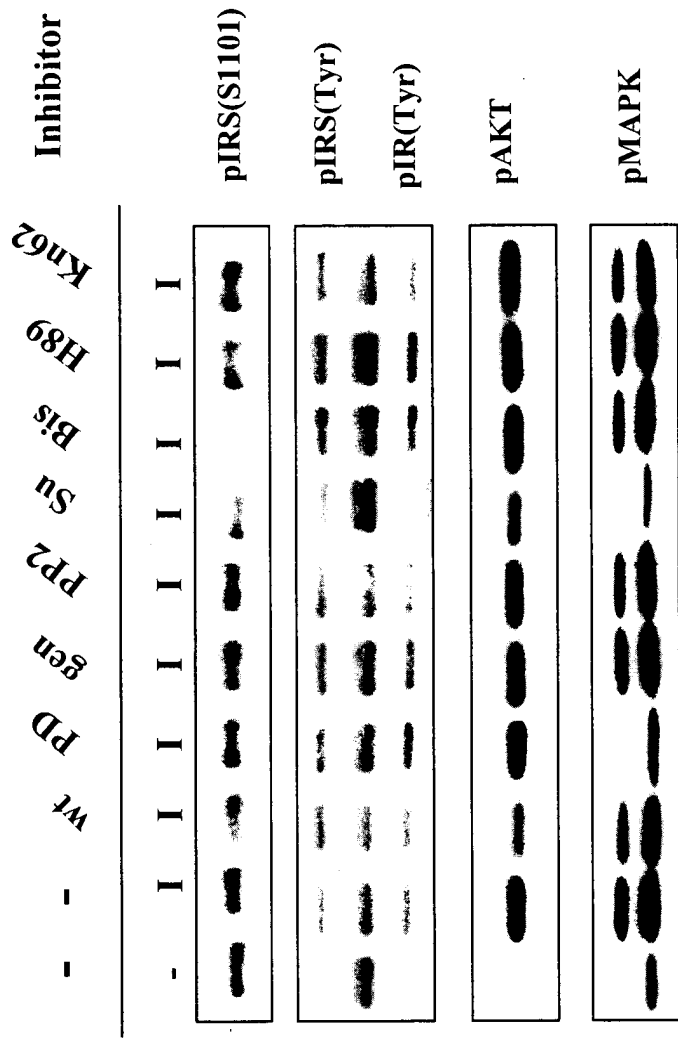


Figure 11: PKCθ kinase phosphorylates IRS-1(Ser1101) in vitro

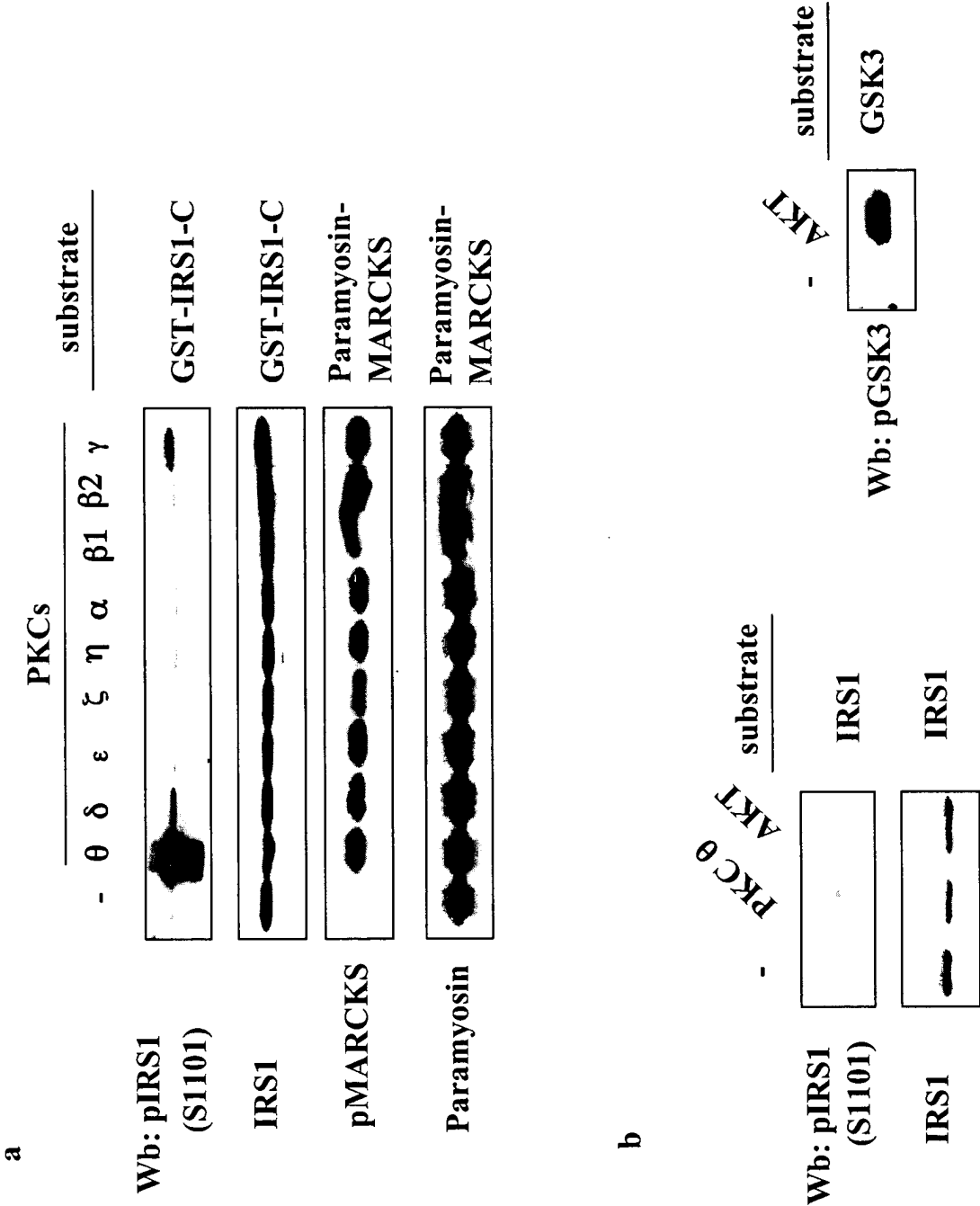
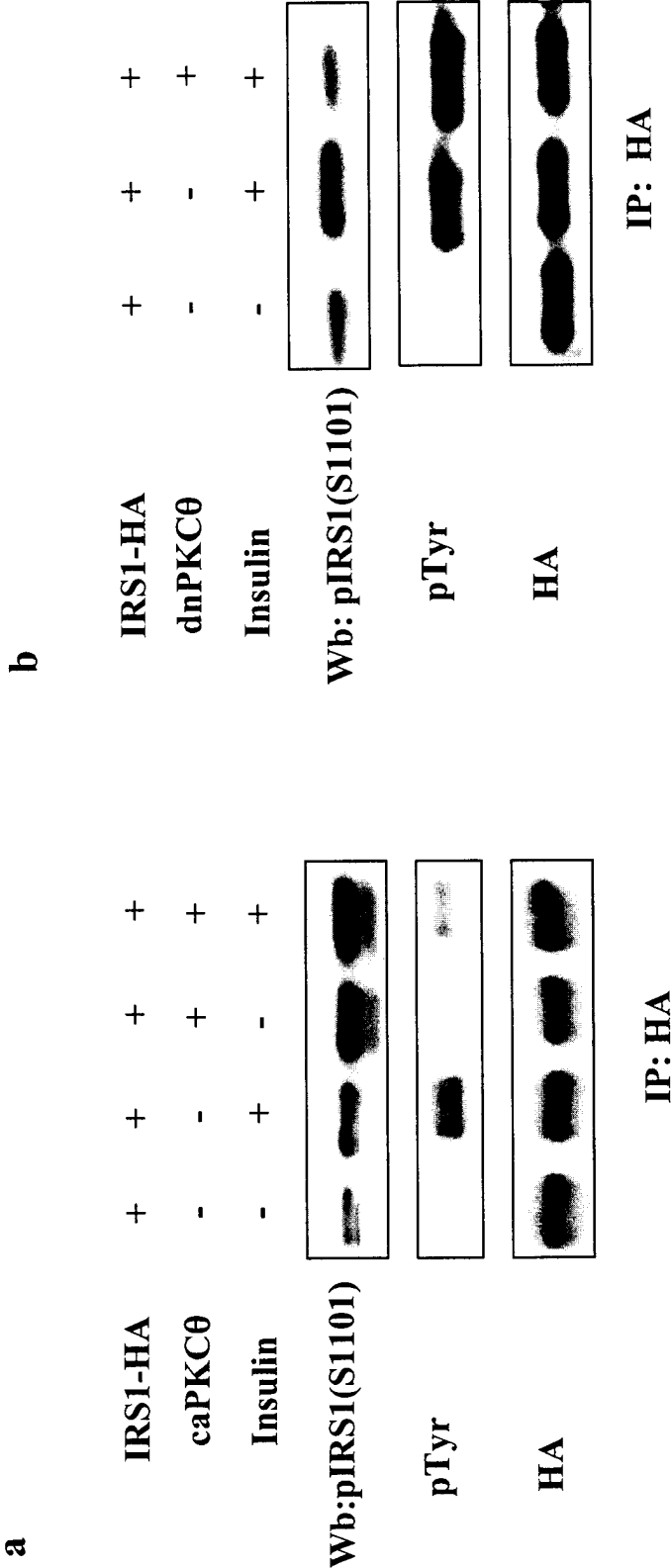


Figure 12: PKCθ kinase phosphorylates IRS-1(Ser1101) in vivo



**Figure 13: Mouse IRS-1 protein sequence (SEQ ID NO: 3)**

1 masppdtdgf sdvrkvgylr kpksmhkrff vlraaseagg parleyyene kkwrhkssap  
61 krsiplescf ninkradskn khlvalytrd ehfaiaadse aeqdswyqal lqlhnrakah  
121 hdgagggcgg scsgssgvge agedlsydtg pgpafkevwq vilkpkglgq tknligiyr  
181 cltsktisfv klseaaavv lqlmnirrcg hsenfffierv grsavgpge fwmqvddsvv  
241 aqnmhetile amramsdefr prsksqssss csnpisvplr rhlhlnppps qvgltrrsrl  
301 esitatpas mvggkpgsfr vrassdgegt msrpsavdgs pvspstnrth ahrhrgssrl  
361 hpplnhrsri pmpssrcsps atspvslsss stsghgtsd clfprssas vsgpsdggf  
421 issdeygssp cdfrssfrsv tpdslghtpp argeeelsny icmggkgast laapnghyil  
481 srggnghryi pganlgtspa lpgdeaagaa dldnrfrkrt hsagtsptis hqktpsqsav  
541 asieeytemm paayppgggs ggrlpgyrhs afvpthsyte eglemhhler rgghhrpds  
601 nlhtddgyp mspgvapvps nrkgngdyp mspksvsapq qiinpirrhp qrvdpngymm  
661 mspsgscspd igggssssss isaapsgssy gkpwtngvgg hthalphak ppvesgggkl  
721 lpctgdymnm spvgdsntss psecygygped pqhkpvlsty slprsfkhtq rpgepegar  
781 hqhlrlssss grlryatae dssstssds lgggycgarp esslthphhh vlqphlprkv  
841 dtaaqtnsrl arptrlsgd pkastlprvr eqqqqqqsssl hppepkspge yvniefgsgq  
901 pgylagpats rsspvrpp qlhpapreet gseymnmdl gpgratwqe sggvelgrig  
961 pappgsatvc rptrsvpnsr gdymtmqigc prqsyvdtsp vapvsyadmr tgiaaekasl  
1021 prptgaapp sstasssvtp qgataeqath sslggpqqp ggmsafrvn lspnhnqsak  
1081 viradtqgcr **rrhssetfsa** ptragntvpf gagaavggsg ggggggsedv krhssasfen  
1141 vwlrpgdlgg vskesapvcg aaggleksln yidldaker sqdcpsqqqs lppppphqpl  
1201 gsnegnspr ssedlsnyas isfqkqpedr q

**Figure 14: Mouse IRS-2 protein sequence (SEQ ID NO: 4)**

1 masaplpgrp asgggdgpnlnnnnnnnnhs vrkcgylrkq khghkrffvl rgpgtggea  
61 saaggspqp prleyyesek kwrsagapk rviadccln inkradakhk yliaitykde  
121 yfavaaeneq eqegwyralt dlvsgrsge gsgtggtgsc saslpvgvg sagaagcddn  
181 yglvtpatav yrevwqvnk pkglgqsknl tgvyrclsa rtigfvklnc egpsvtlqln  
241 nirrcghsds fffievgrsa vtgpgelwmq addsvvaqni hetileamka lkelfefrpr  
301 sksqssgssa thpivpgr rhhhlvnlpp sqtglvrrsr tdsaatppa akctscrvt  
361 asegdggaag gagtaggrpm svagsplspg pvrapsrsh tlasgaggrp skvtlapagg  
421 alqhsrsnsm pvahsppaat spgslssssg hgsgsyplpp gshphlphpl hhpqgqrps  
481 gsasasgsp dpgfmsldey gsspgdlraf sshrsntpes iaetppardg sggylygms  
541 mdrplshcgr pyrvsgdga qldrglrkr tysltparq rvpqpssas ldeytlmrat  
601 fsgssgrlcp sfpasspkva ynpypedygd ieigshksss snlgaddgym pmtpgaals  
661 ggpnscksdd ympmsptsvs apkqilqprl aaalppsgaa vpappsgvgr tfpvngggyk  
721 asspaesspe ds gymrmwgc sklsmenpdp klpngdyn kspseagtag tpdfsaalr  
781 ggseglkgip ghcysslprs ykapcscsgd ndqyvlmssp vgrileeerl epqatpgagt  
841 fgaaggshtq phhsavpssm rpsaiggrpe gflgqrcrav rptrlslegl qtlpsmqeyp  
901 lptepkspge yinidpgeag trlspapppl lasaasssl lsasspassl gsgtpgtssd  
961 srqrsplsdymnldpsspks pkpstrsgdt vgsmdgllsp easspypplp prpstspss  
1021 qqplppapgd lyrlppasaa tsqgptagss mssepdgndg ysemafvaat tppqpivapp  
1081 kpegarvasp tsglkrslm dqvsgveafl qvsqppdphr gkviradpq **ggrrrhsset**  
1141 **fsstttvtpv** spsfahnscr hnsasvenvs lrkssegsst lgggdeppts pgqaqplvav  
1201 ppvpqarpwn pgqpgalgc pggssspmrr etsvgfqngl nyiaidvrge qgslaqsqq  
1261 pgdknswsr rslggllgtv ggsgasgvcg gpgtgalpsa styasidfls hhlkeatvvk  
1321 e